REMARKS

Reconsideration is requested.

Claims 12, 13, 14, 16-22 and 29-32 are pending. Claims 30-32 have been added to define further patentable aspects of the disclosed invention. Support may be found throughout the specification. No new matter has been added.

The Section 103 rejection of claims 12-14, 16-22 and 29 over Petyaev (WO 03/017992) and Shiff (U.S. Patent No. 6,201,028) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The Examiner asserts that "Shiff et al disclose a strong correlation between atherosclerosis and hyperlipidemia" and that a person of ordinary skill in the art would have allegedly been motivated by Shiff to use the compositions disclosed by Petyaev to treat hyperlipidemia.

The Examiner is requested however to indicate where Shiff describes such a "strong correlation" between atherosclerosis and hyperlipidemia. The applicants believe that Shiff teaches that hyperlipidemia is a risk factor for atherosclerosis. This is very different from a teaching of a correlation which would have been sufficient to motivate an ordinarily skilled person to use the anti-atherosclerosis compositions disclosed by Petyaev to treat hyperlipidemia.

The applicants believe that this is apparent from, for example, column 5 lines 15-17 of Shiff, which state that:

> "... many factors are associated with coronary heart disease and the acceleration of atherosclerosis..." .

Shiff continues as follows at column 5, lines 18-21:

> "The most important risk factors are advanced age, elevated plasma cholesterol and low density lipoprotein cholesterol, high arterial blood pressure, diabetes and cigarette smoking. "

One of ordinary skill therefore learns from Shiff that there are a number of important risk factors for atherosclerosis and these include elevated plasma cholesterol and low density lipoprotein cholesterol, as well as advanced age, high blood pressure, diabetes and smoking.

The applicants believe however that this fails to rise to the level of teaching a "strong correlation" sufficient to have motivated one of ordinary skill to have used a composition disclosed by Petyaev to treat hyperlipidemia, because the ordinarily skilled person would have had no reason to expect or predict that compositions which treat a disease pathology, such as atherosclerosis, would have any effect on a risk factor such as elevated plasma cholesterol and low density lipoprotein cholesterol, age, high blood pressure, diabetes and smoking.

The applicants believe that the nature of the relationship between a risk factor and a disease pathology taught in the cited art is such that there would have been no reason to have expected or reasonably predicted that the treatment of the disease pathology would have an effect on the risk factor. For example, the applicants believe that the ordinarily skilled person would not have expected that the treatment of atherosclerosis would have any effect on advanced age, high blood pressure, diabetes or smoking, even though Shiff teaches that these are important risk factors for atherosclerosis. In the same way, the applicants submit that there was no reason for the

ordinarily skilled person to have expected any effect on elevated plasma cholesterol or low density lipoprotein cholesterol. On the basis of Shiff, there was no reason for one of ordinary skill to have predicted that the anti-atherosclerosis compositions of Petyaev would have been reasonably expected to be useful in the treatment of either hyperlipidemia or any of the other important risk factors set out in Shiff.

In particular, the applicants believe that the ordinarily skilled person would have had no reason to expect that compositions which treat the disease pathology via a specific mechanism of action would have had any effect on risk factors (or other parameters) which are not associated with that mechanism of action. For example, Petyaev teaches that the disclosed compositions treat atherosclerosis by inhibiting lipid oxidizing anti-Chlamydia abzymes. Lipid oxidizing anti-Chlamydia abzymes were not associated in the cited art with any of the important risk factors set out in Shiff (i.e. advanced aging, elevated plasma cholesterol and low density lipoprotein cholesterol, high arterial blood pressure, diabetes or cigarette smoking). In the absence of any association with lipid oxidizing anti-Chlamydia abzymes, for example, a person having ordinary skill in the art would not have expected the anti-atheroslcerosis compositions of Petyaev to have had any effect on any of these risk factors and there would have been no motivation to attempt to employ them to ameliorate any of these risk factors.

The applicants further submit that Shiff et al does not contain any teaching which would have suggested to the ordinarily skilled person that the Petyaev compositions would have had any effect on hyperlipidemia. The applicants understand Shiff to teach that atherosclerosis is treated by

> "... inducing or stimulating apoptosis, reducing proliferation, inducing quiescence inhibiting cell migration or influencing cell differentiation of the cells in the vessel wall that contribute to arterial lesions." See column 1, lines 13-17 of Shiff.

Shiff also teaches that atherosclerosis is assessed by measuring vessel wall thickness in a mouse model (Table 2).

The applicants believe that Shiff clearly regards hyperlipidemia and atherosclerosis as separate and distinct conditions, the former being measured by total serum cholesterol levels and the latter by vessel wall thickness. While Shiff teaches that aspirin lowers the plasma cholesterol levels relative to controls in ApoE knockout mice (column 10 lines 58-67), Shiff further teaches that aspirin has no significant effect on atherogenesis in these mice (column 11 lines 14-16). In ApoE knockout mice, aspirin is therefore shown to affect lipid metabolism without affecting atherogenesis.

Furthermore, not only does Shiff fail to teach that aspirin is useful in the treatment of atherosclerosis, but Shiff also fails to teach that aspirin is useful in the treatment of hyperlidemia. Shiff teaches that aspirin lowers the plasma cholesterol levels relative to controls in ApoE knockout mice but this does not equate to a teaching of treatment of hyperlipidemia with aspirin because i) the mean body weight of the treated mice was less than the controls anyway (ii) the only effects were observed in mice which were ApoE deficient and (iii) there is no suggestion that the effect of aspirin on total cholesterol was statistically significant (unlike the effect of Sulindac).

The applicants submit that the ordinarily skilled person would therefore find no teaching in Shiff that any correlation of atherosclerosis and hyperlipidemia is sufficiently

"strong" to have led to an expectation that the anti-atherosclerosis compositions of Petyaev would have been reasonably expected to treat hyperlipidemia.

Withdrawal of the Section 103 rejection of claims 12-14, 16-22 and 29 over Petyaev (WO03/017992) in view of Shiff et al (U.S. Patent No. 6,201,028) is requested.

The Section 103 rejection of claims 12-14, 16-22 and 29 over Klein (U.S. Patent No. 6,174,865) and Shiff (U.S. Patent No. 6,201,028) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The Examiner is understood to believe that because Shiff teaches treatment of hyperlipidemia with aspirin and Klein teaches treatment of hyperlipidemia with azithromycin, it would have allegedly been obvious for the ordinarily skilled person to have used a combination of the two for the treatment of hyperlipidemia.

For the reasons set out above, the applicants again note that Shiff does not teach treatment of hyperlipidemia with aspirin. Shiff is undersood by the applicants to teach that aspirin lowered the plasma cholesterol levels relative to controls in ApoE knockout mice (column 10, lines 58-67). However, this does not equate to a teaching of treatment of hyperlipidemia with aspirin because (i) the mean body weight of the treated mice was less than the controls anyway, (ii) the only effects were observed in mice which were ApoE deficient, (iii) there is no suggestion that the effect of aspirin on total cholesterol was statistically significant (whereas the effect of Sulindac is clearly stated to be statistically significant), and (iv) there is no suggestion of any effect on other lipid parameters.

The applicants understand Klein to specifically teach the treatment of hypertriglyceridemia and that Figures 1 and 2 of Klein show that other lipid parameters, such as LDL or total cholesterol, are unaffected by this treatment.

The present invention relates to the finding that treating human patients with combination of a metal chelator and an anti-microbial compound leads to a significant reduction in total cholesterol which persists for at least 2m following treatment (see Table 3 and page 13 lines 5 to 13). Furthermore, levels of apolipoprotein B are also significantly reduced without any concomitant reduction in LDL cholesterol levels (see Table 3 and page 13 lines 15 to 24). The ordinarily skilled person would find these results both unexpected and unpredictable in view of the cited art, since they are not observed when either compound is used alone.

The combination of metal chelator and an anti-microbial compound therefore yields unpredictable results which would not have been obvious from Klein or Shiff or their combination and which would not have been be obtained using either compound individually.

Withdrawal of the Section 103 rejection of claims 12-14, 16-22 and 29 over Klein and Shiff et al is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required.

Respectfully submitted,

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